

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Tarara et al.	Group Art Unit: 1618
Application No: 10/750,934 Confirmation No: 1899	Examiner: Schlientz, Leah H
Filed: December 31, 2003	Attorney Docket No: 53279-US-CNT (NV.0101.00)
Title: PHARMACEUTICAL FORMULATION WITH AN INSOLUBLE ACTIVE AGENT	January 25, 2010 San Francisco, California

**APPEAL BRIEF**

VIA ELECTRONIC FILING

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Examiner:

In response to the Examiner's Final Rejection of June 25, 2009 and the Notice of Appeal filed on September 24, 2009, the Applicant of the above-referenced patent application (hereinafter Appellant) hereby appeals to the Board of Patent Appeals and Interferences. Appellant requests the reversal of the Final Rejection.

**Certificate of Transmission**

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By:

  
Melanie Hitchcock

Date: January 25, 2010

**(1) *Real Party in Interest***

The real party in interest of the present application is Novartis AG (by way of assignment from Novartis Pharmaceuticals AG and from Nektar Therapeutics, which was formerly Inhale Therapeutic Systems, Inc.), having a place of business at Forum 1, Novartis Campus, CH-4056 Basel, Switzerland.

**(2) *Related Appeals and Interferences***

Appellant, Appellant's legal representative, and assignee are aware of no appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

**(3) *Status of Claims***

Claims 38, 39, 41, 44, 47-56, 58, 60, 62-68, 103-105 and 109-111 are presently pending in the case. Claims 38, 39, 41, 44, 47-56, 58, 60, 62-68, 103-105 and 109-111 have been finally rejected. The rejection of each of claims 38, 39, 41, 44, 47-56, 58, 60, 62-68, 103-105 and 109-111 is hereby appealed.

Claims 1-37, 40, 42, 43, 45, 46, 57, 59, 61, 69-102 and 106-108 have been cancelled.

**(4) *Status of Amendments***

No amendments have been filed after Final Office Action. Accordingly, all amendments submitted during prosecution have been entered.

**(5) Summary of the Claimed Subject Matter**

As recited in claim 38, discussed in the specification and shown in Figures 1-7, a pharmaceutical formulation for pulmonary administration comprises particulates comprising active agent particles in a matrix comprising a phospholipid (page 13 line 26 through page 16 line 16). The active agent particles having a geometric diameter of less than about 3  $\mu\text{m}$  (page 12 line 1-23, page 13 lines 5-16) and a solubility in water of about 0.1 to about 1.0 mg/ml (page 11 lines 9-29). The active agent particles are dispersed within the phospholipid matrix. The particulates are porous, have a mass median diameter less than 20  $\mu\text{m}$  (page 20 line 6), a bulk density of less than about 0.5 g/cm<sup>3</sup> (page 23 line 16), and a mass median aerodynamic diameter less than about 2.6  $\mu\text{m}$  (page 34 line 4). The particulates do not comprise lactose.

As recited in claim 54, a pharmaceutical formulation for pulmonary administration comprises particulates comprising amphotericin B (page 32-38) particles in a matrix comprising a phospholipid (page 13 line 26 through page 16 line 16) wherein the amphotericin B particles have a solubility in water of about 0.1 to about 1.0 mg/ml, and are dispersed within the phospholipid matrix. The particulates are porous, have a mass median diameter less than 20  $\mu\text{m}$  (page 20 line 6), a bulk density of less than about 0.5 g/cm<sup>3</sup> (page 23 line 16), and a mass median aerodynamic diameter less than about 2.6  $\mu\text{m}$  (page 34 line 4). The particulates do not comprise lactose.

As recited in claim 104, a pharmaceutical formulation in dry powder form for aerosolization and pulmonary administration comprises an active agent particle having a geometric diameter of less than about 3  $\mu\text{m}$  (page 12 line 1-23, page 13 lines 5-16) and a solubility in water of about 0.1 to about 1.0 mg/ml (page 11 line 9-19) or a glass transition temperature of about 283°C. The active agent particle is substantially within a porous phospholipid matrix (page 13 line 26 through page 16 line 16). The pharmaceutical formulation is formed by preparing a feedstock comprising active agent particles and one or more phospholipids, and spray-drying the feedstock to produce porous particulates (page 19 lines 11-20) having a mass median diameter less than 20

µm (page 20 line 6), a bulk density of less than about 0.5 g/cm<sup>3</sup> (page 23 line 16) and a mass median aerodynamic diameter less than about 2.6 µm (page 34 line 4). The particulates do not comprise lactose.

**(6) *Grounds of Rejection to be Reviewed on Appeal***

Appellant requests review of the Examiner's following grounds of rejection:

Claims 38, 39, 41, 44, 47-56, 58, 60, 62-68, 103-105 and 109-111 have been rejected under 35 U.S.C. §103(a) as being unpatentable over WO 01/85136 to Weers et al (hereinafter Weers et al), as evidenced by US 2002/0177562 to Weickert et al (hereinafter Weickert et al), 2000 Journal article to Weidmann et al (hereinafter Weidmann et al) and WO 00/01365 to Didriksen (hereinafter Didriksen).

Claims 38, 39, 41, 44, 47-56, 58, 60, 62-68, 103-105 and 109-111 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent Application No. 11/187,757.

## **(7) Argument**

Appellant believes each of claims 38, 39, 41, 44, 47-56, 58, 60, 62-68, 103-105 and 109-111 are improperly rejected and are therefore allowable for the following reasons:

### The rejections under §103(a) are improper

The Examiner's rejection of claims 38, 39, 41, 44, 47-56, 58, 60, 62-68, 103-105 and 109-111 under 35 USC §103(a) as being unpatentable over Weers et al as evidenced by Weickert et al, Weidmann et al and Didriksen is improper and should be reversed.

### **Independent claim 38**

Weers et al, Weickert et al, Wiedmann et al, and Didriksen do not render independent claim 38 unpatentable. Claim 38 is to a pharmaceutical formulation comprising particulates comprising active agent particles in a matrix comprising a phospholipid, wherein the particulates do not comprise lactose. The active agent particles have a geometric diameter of less than about 3  $\mu\text{m}$  and a solubility in water of about 0.1 to about 1.0 mg/ml. Weers et al does not disclose particulates comprising active agent particles of the type claimed in a matrix comprising a phospholipid, wherein the particulates do not comprise lactose. Instead, Weers et al discloses particulates where a solution of an active agent (as opposed to particles of active agent) is dispersed within a phospholipid matrix. The solution is spray dried to create particulates where the active agent is dispersed within the particulate, but not as particles that have a solubility in water of about 0.1 to about 10 mg/ml.

Weers et al Example V is an exception to the above. In Example V, Weers et al discloses budesonide particles that are in a phospholipid matrix. However, in this example, the budesonide is combined with lactose (see page 12 lines 1-4). Claim 38

explicitly excludes lactose-containing particles from its ambit. Accordingly, Weers et al does not disclose, teach or suggest the invention as set forth in claim 38.

In the Final Office Action of June 25, 2009, the Examiner contends that it would have been obvious to one of ordinary skill in the art to eliminate lactose carrier particles from the Example V version of Weers et al. However, there are no lactose carrier particles in Example V of Weers et al. Lactose carrier particles are large particles that are sometimes used in dry powder compositions. As noted by the Examiner, Weers et al developed a dry powder that does not need large lactose carriers. Example V is one example of a Weers et al formulation that does not need and does not have large lactose carriers. However, Example V does have lactose, not as a carrier but as component of a solution used for suspending the budesonide particles for spray drying (see page 27 lines 1-9). Thus, the Examiner's contention that it would have been obvious to remove lactose carrier particles is completely without moment since there are no lactose carrier particles in Weers et al Example V. The Examiner has not accounted for the lactose that is present in the feedstock that is spray dried to form the particulates. Since that lactose is still present in the formulation, the Examiner has failed to establish a *prima facie* case under 35 U.S.C. §103(a). In fact, it would not have been obvious to one of ordinary skill in the art to modify a single example of Weers et al in a manner that would arrive at Appellant's invention, particularly in the absence of any motivation to do so.

Weickert et al, Weidmann et al, and Didriksen are not relied upon to make up for this deficiency of Weers et al, nor do they. Accordingly, claim 38 is allowable over the combination of references.

For at least these reasons, claim 38 is not properly rejectable under 35 USC §103(a) as being unpatentable over Weers et al, Weickert et al, Wiedmann et al, and Didriksen. The modification proposed by the Examiner is not one that would have been well within the grasp of one of ordinary skill in the art at the time the invention was made. In this regard, the Examiner has failed to establish that the teachings of Weickert

et al, Wiedmann et al, and Didriksen could be applied, with a reasonable likelihood of success, to Weers et al in a manner that would result in the invention of claim 38. There is no evidence to suggest that this is a situation where the ordinary artisan could have combined in the teachings in a manner that would result in the invention of claim 38, and there is no evidence to suggest the artisan would have seen the benefit in doing so. Thus, claim 38 is allowable over the references cited.

Appellant requests reversal of the rejection of claim 38 under 35 U.S.C. §103(a). In addition, Appellant requests reversal of the rejection of claims 39, 41, 44, 47-53 and 103 which depend from claim 38 and are not rendered unpatentable by Weers et al, Weickert et al, Wiedmann et al, and Didriksen for at least the same reasons as claim 38.

#### **Independent claim 54**

In addition, Weers et al, Weickert et al, Wiedmann et al, and Didriksen do not render independent claim 54 unpatentable. Claim 54 is to a pharmaceutical formulation comprising particulates comprising amphotericin B particles in a matrix comprising a phospholipid, wherein the particulates do not comprise lactose. Weers et al does not disclose particulates comprising active agent particles in a matrix comprising a phospholipid, wherein the particulates do not comprise lactose. Instead, Weers et al discloses particulates where a solution of an active agent (as opposed to particles of active agent) is dispersed within a phospholipid matrix. As discussed above, in one example, Weers et al discloses budesonide particles within a matrix (see Example V). However, in this example, the budesonide is combined with lactose. Claim 54 explicitly excludes lactose-containing particles from its ambit. Accordingly, Weers et al does not disclose, teach or suggest the invention as set forth in claim 54. Weickert et al, Weidmann et al, and Didriksen do not make up for the deficiencies of Weers et al. Therefore, the Examiner has failed to establish a *prima facie* case under 35 U.S.C. §103(a).

For at least these reasons, claim 54 is not properly rejectable under 35 USC §103(a) as being unpatentable over Weers et al, Weickert et al, Wiedmann et al, and Didriksen. The modification proposed by the Examiner is not one that would have been well within the grasp of one of ordinary skill in the art at the time the invention was made. In this regard, the Examiner has failed to establish that the teachings of Weickert et al, Wiedmann et al, and Didriksen could be applied, with a reasonable likelihood of success, to Weers et al. There is no evidence to suggest that this is a situation where the ordinary artisan could have combined in the teachings in a manner that would result in the invention of claim 54, and there is no evidence to suggest the artisan would have seen the benefit in doing so. Thus, claim 54 is allowable over the references cited.

Appellant requests reversal of the rejection of claim 54 under 35 U.S.C. §103(a). In addition, Appellant requests reversal of the rejection of claims 55, 56, 58, 60 and 62-68 which depend from claim 38 and are not rendered unpatentable by Weers et al, Weickert et al, Wiedmann et al, and Didriksen for at least the same reasons as claim 54.

#### **Independent claim 104**

Weers et al, Weickert et al, Wiedmann et al, and Didriksen do not render independent claim 104 unpatentable, either. Claim 104 is to a pharmaceutical formulation comprising an active agent particle in a phospholipid matrix, wherein the particulates do not comprise lactose. Weers et al does not disclose particulates comprising active agent particles in a matrix comprising a phospholipid, wherein the particulates do not comprise lactose. Instead, Weers et al discloses particulates where a solution of an active agent (as opposed to particles of active agent) is dispersed within a phospholipid matrix. As discussed above, in one example, Weers et al discloses budesonide particles within a matrix (see Example V). However, in this example, the budesonide is combined with lactose. Claim 104 explicitly excludes lactose-containing particles from its ambit. Accordingly, Weers et al does not disclose, teach or suggest the invention as set forth in claim 104. Weickert et al, Weidmann et al, and Didriksen do

not make up for the deficiencies of Weers et al. Therefore, the Examiner has failed to establish a *prima facie* case under 35 U.S.C. §103(a).

For at least these reasons, claim 104 is not properly rejectable under 35 USC §103(a) as being unpatentable over Weers et al, Weickert et al, Wiedmann et al, and Didriksen. The modification proposed by the Examiner is not one that would have been well within the grasp of one of ordinary skill in the art at the time the invention was made. In this regard, the Examiner has failed to establish that the teachings of Weickert et al, Wiedmann et al, and Didriksen could be applied, with a reasonable likelihood of success, to Weers et al. There is no evidence to suggest that this is a situation where the ordinary artisan could have combined in the teachings in a manner that would result in the invention of claim 104, and there is no evidence to suggest the artisan would have seen the benefit in doing so. Thus, claim 104 is allowable over the references cited.

Appellant requests reversal of the rejection of claim 104 under 35 U.S.C. §103(a). In addition, Appellant requests reversal of the rejection of claim 105 which depends from claim 104 and is not rendered unpatentable by Weers et al, Weickert et al, Wiedmann et al, and Didriksen for at least the same reasons as claim 104.

#### The double patenting rejections

The Examiner provisionally rejected claims 38, 39, 41, 44, 47-56, 58, 60, 62-68, 103-105 and 109-111 under the judicially created doctrine of double patenting as being unpatentable over the claims of U.S. Patent Applications 11/187,757.

Appellant will file terminal disclaimers as appropriate upon the indication of otherwise allowable claims.

## Conclusion

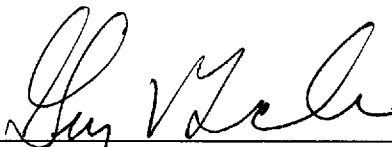
Thus, it is believed that all rejections made by the Examiner have been addressed and overcome by the above arguments. Therefore, all pending claims are allowable. A reversal is respectfully requested.

Should there be any questions, Appellant's representative may be reached at the number listed below.

Respectfully submitted,

JANAH & ASSOCIATES

Dated: January 25, 2010

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## **(8) Claims Appendix**

38. A pharmaceutical formulation for pulmonary administration, the pharmaceutical formulation comprising:

particulates comprising active agent particles in a matrix comprising a phospholipid, the active agent particles having a geometric diameter of less than about 3  $\mu\text{m}$  and a solubility in water of about 0.1 to about 1.0 mg/ml and wherein the active agent particles are dispersed within the phospholipid matrix; and

wherein the particulates are porous, have a mass median diameter less than 20  $\mu\text{m}$ , a bulk density of less than about 0.5 g/cm<sup>3</sup>, a mass median aerodynamic diameter less than about 2.6  $\mu\text{m}$ , and wherein the particulates do not comprise lactose.

39. A pharmaceutical formulation according to claim 38 wherein the formulation provides for the delivery to the lung of a dose of at least about 5 mg in a single inhalation.

41. A pharmaceutical formulation according to claim 38 wherein a formulation fine particle fraction of less than 3.3  $\mu\text{m}$  is at least about 72 percent.

44. A pharmaceutical formulation according to claim 38 wherein the matrix comprises one or more of dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, diarachidoylphosphatidylcholine, dibehenoylphosphatidylcholine, diphosphatidyl glycerol, short-chain phosphatidylcholines, long-chain saturated phosphatidylethanolamines, long-chain saturated phosphatidylserines, long-chain saturated phosphatidylglycerols, and long-chain saturated phosphatidylinositols.

47. A pharmaceutical formulation according to claim 38 wherein the particulates have a bulk density less than 0.3 g/cm<sup>3</sup>.

48. A pharmaceutical formulation according to claim 38 wherein the particulates have a bulk density less than  $0.2 \text{ g/cm}^3$ .
49. A pharmaceutical formulation according to claim 38 wherein the particulates are in a dry powder form for aerosolization in a dry powder inhaler.
50. A pharmaceutical formulation according to claim 38 wherein the particulates are suspended in a propellant for aerosolization in a metered dose inhaler.
51. A pharmaceutical formulation according to claim 38 wherein the particulates are suspended within a liquid for aerosolization in a nebulizer.
52. A pharmaceutical formulation according to claim 38 wherein the particulates further comprise a polyvalent cation.
53. A pharmaceutical formulation according to claim 38 wherein the particulates are formed by spray drying with a blowing agent.
54. A pharmaceutical formulation for pulmonary administration, the pharmaceutical formulation comprising:  
particulates comprising amphotericin B particles in a matrix comprising a phospholipid wherein the amphotericin B particles have a solubility in water of about 0.1 to about 1.0 mg/ml, and are dispersed within the phospholipid matrix, and;  
wherein the particulates are porous, have a mass median diameter less than  $20 \text{ }\mu\text{m}$ , a bulk density of less than about  $0.5 \text{ g/cm}^3$  and a mass median aerodynamic diameter less than about  $2.6 \text{ }\mu\text{m}$ , and wherein the particulates do not comprise lactose.
55. A pharmaceutical formulation according to claim 54 wherein the particulates have a mass median diameter less than  $10 \text{ }\mu\text{m}$ .

56. A pharmaceutical formulation according to claim 54 wherein the particulates have a mass median diameter less than 5  $\mu\text{m}$ .

58. A pharmaceutical formulation according to claim 54 wherein the amphotericin B particles are crystalline.

60. A pharmaceutical formulation according to claim 54 wherein the lipid matrix comprises one or more of dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, diarachidoylphosphatidylcholine, dibehenoylphosphatidylcholine, diphosphatidyl glycerol, short-chain phosphatidylcholines, long-chain saturated phosphatidylethanolamines, long-chain saturated phosphatidylserines, long-chain saturated phosphatidylglycerols, and long-chain saturated phosphatidylinositols.

62. A pharmaceutical formulation according to claim 54 wherein the particulates have a bulk density less than 0.3  $\text{g}/\text{cm}^3$ .

63. A pharmaceutical formulation according to claim 54 wherein the particulates have a bulk density less than 0.2  $\text{g}/\text{cm}^3$ .

64. A pharmaceutical formulation according to claim 54 wherein the particulates are in dry powder form for aerosolization in a dry powder inhaler.

65. A pharmaceutical formulation according to claim 54 wherein the particulates are suspended in a propellant for aerosolization in a metered dose inhaler.

66. A pharmaceutical formulation according to claim 54 wherein the particulates are suspended within a liquid for aerosolization in a nebulizer.

67. A pharmaceutical formulation according to claim 54 wherein the particulates further comprise a polyvalent cation.

68. A pharmaceutical formulation according to claim 54 wherein the particulates are formed by spray drying with a blowing agent.

103. A pharmaceutical formulation according to claim 38 wherein the active agent comprises ciprofloxacin.

104. A pharmaceutical formulation in dry powder form for aerosolization and pulmonary administration, the pharmaceutical formulation comprising:

an active agent particle having a geometric diameter of less than about 3  $\mu\text{m}$  and a solubility in water of about 0.1 to about 1.0 mg/ml or a glass transition temperature of about 283°C;

a porous phospholipid matrix wherein the active agent particle is substantially within the phospholipid matrix; and

wherein the pharmaceutical formulation is formed by preparing a feedstock comprising active agent particles and one or more phospholipids, and spray-drying the feedstock to produce porous particulates having a mass median diameter less than 20  $\mu\text{m}$ , a bulk density of less than about 0.5 g/cm<sup>3</sup> and a mass median aerodynamic diameter less than about 2.6  $\mu\text{m}$ , and wherein the particulates do not comprise lactose.

105. A pharmaceutical formulation according to claim 104 wherein the particulates have a bulk density less than 0.3 g/cm<sup>3</sup>.

109. A pharmaceutical formulation according to claim 38 wherein the particles consist essentially of the active agent.

110. A pharmaceutical formulation according to claim 54 wherein the amphotericin B particles consist essentially of amphotericin B.

111. A pharmaceutical formulation according to claim 104 wherein the active agent particles consist essentially of the active agent.

**(9) Evidence Appendix**

none

**(10) Related Proceedings Appendix**

none